The Phenotype and Genotype of Mevalonate Kinase Deficiency: A Series of 114 Cases From the Eurofever Registry

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Abstract: OBJECTIVE:Mevalonate kinase deficiency (MKD) is a rare metabolic disease characterized by recurrent inflammatory episodes. This study was undertaken to describe the genotype, phenotype, and response to treatment in an international cohort of MKD patients. METHODS:All MKD cases were extracted from the Eurofever registry (Executive Agency for Health and Consumers project no. 2007332), an international, multicenter registry that retrospectively collects data on children and adults with autoinflammatory diseases. RESULTS:The study included 114 MKD patients. The median age at onset was 0.5 years. Patients had on average 12 episodes per year. Most patients had gastrointestinal symptoms (n = 112), mucocutaneous involvement (n = 99), lymphadenopathy (n = 102), or musculoskeletal symptoms (n = 89). Neurologic symptoms included headache (n = 43), cerebellar syndrome (n = 2), and mental retardation (n = 4). AA amyloidosis was noted in 5 patients, almost twice as many as expected from findings in previous cohorts. Macrophage activation syndrome occurred in 1 patient. Patients were generally well between attacks, but 10-20% of the patients had constitutional symptoms, such as fatigue, between fever episodes. Patients with p.V377I/p.I268T compound heterozygosity had AA amyloidosis significantly more often. Patients without a p.V377I mutation more often had severe musculoskeletal involvement. Treatment with nonsteroidal antiinflammatory drugs relieved symptoms. Steroids given during attacks, anakinra, and etanercept appeared to improve symptoms and could induce complete remission in patients with MKD. CONCLUSION:We describe the clinical and genetic characteristics of 114 MKD patients, which is the largest cohort studied so far. The clinical manifestations confirm earlier reports. However, the prevalence of AA amyloidosis is far higher than expected.

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The Phenotype and Genotype of Mevalonate Kinase Deficiency

A Series of 114 Cases From the Eurofever Registry

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Objective. **Mevalonate kinase deficiency (MKD) is a rare metabolic disease characterized by recurrent inflammatory episodes. This study was undertaken to describe the genotype, phenotype, and response to treatment in an international cohort of MKD patients.**

Methods. **All MKD cases were extracted from the Eurofever registry (Executive Agency for Health and Consumers project no. 2007332), an international, multicenter registry that retrospectively collects data on children and adults with autoinflammatory diseases.**

Results. **The study included 114 MKD patients. The median age at onset was 0.5 years. Patients had on average 12 episodes per year. Most patients had gastrointestinal symptoms (n = 112), mucocutaneous involvement (n = 99), lymphadenopathy (n = 102), or musculoskeletal symptoms (n = 89). Neurologic symptoms included headache (n = 43), cerebellar syndrome (n = 2), and mental retardation (n = 4). AA amyloidosis was noted in 5 patients, almost twice as many as expected from findings in previous cohorts. Macrophage activation syndrome occurred in 1 patient. Patients were generally well between attacks, but 10–20% of the patients had constitutional symptoms, such as fatigue, between fever episodes. Patients with p.V377I/p.I268T compound heterozygosity had AA amyloidosis significantly more often. Patients**

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without a p.V377I mutation more often had severe musculoskeletal involvement. Treatment with nonsteroidal anti-inflammatory drugs relieved symptoms. Steroids given during attacks, anakinra, and etanercept appeared to improve symptoms and could induce complete remission in patients with MKD.

Conclusion. **We describe the clinical and genetic characteristics of 114 MKD patients, which is the largest cohort studied so far. The clinical manifestations confirm earlier reports. However, the prevalence of AA amyloidosis is far higher than expected.**

Mevalonate kinase deficiency (MKD) is a rare autoinflammatory syndrome characterized by fever and generalized inflammation. The disease encompasses a continuum of 2 phenotypes, known as hyperimmunoglobulinemia D with periodic fever syndrome (HIDS; MIM no. #260920) and mevalonic aciduria (MA; MIM no. #610377) (1–4). Patients with MKD present with fever, gastrointestinal (GI) symptoms, lymphadenopathy, arthralgia, myalgia, skin rash, and mucosal ulcers. Furthermore, patients with the more severe phenotype mevalonic aciduria can also exhibit dysmorphic features, prenatal and postnatal growth retardation, and neurologic and ocular involvement (5).

Both phenotypes are caused by mutations in the *MVK* gene (6,7). This gene encodes mevalonate kinase, an enzyme that is part of the mevalonate pathway. This pathway produces cholesterol and unsaturated lipid chains, known as nonsterol isoprenoids (8). Mevalonate kinase activity is reduced in MKD patients, varying from 1.8% to 28% of the activity seen in healthy controls in patients with the HIDS phenotype, to below 0.5% in patients affected by the MA phenotype, although overlap occurs (6,9,10). The substrate of this enzyme, mevalonic acid, accumulates and is excreted in the urine. Patients with MKD therefore often excrete elevated amounts of mevalonic acid (10–14). Due to the lack of clinical criteria, patients can only be diagnosed by the identification of 2 pathogenic *MVK* mutations or by detection of decreased enzyme activity (15).

The first MKD patients were described in 1984 (2). Several hundred patients with this rare disease have been identified to date. MKD has been more frequently reported in patients with Caucasian ethnicity; a disproportionate number of Dutch HIDS patients have been described, probably due to the presence of a founder mutation (p.V377I) in this population (16). The current number of MKD patients is certainly an underestimate, as many patients remain undiagnosed (8). Since many physicians are still not familiar with this disease, the mean diagnostic delay is 7.1 years (17). MKD patients are often believed to have other diseases, such as infections, immunodeficiency, or other autoinflammatory syndromes, before being diagnosed correctly (17).

This study aimed to describe the clinical and genetic characteristics and the response to treatment in a large, international cohort in order to increase knowledge about this rare disease and hence facilitate diagnosis and inform discussion of treatment and prognosis with affected families.

PATIENTS AND METHODS

Patients. All patients were enrolled in the Eurofever registry (Executive Agency for Health and Consumers project no. 2007332), an international, multicenter registry that retrospectively collects information on patients with autoinflammatory diseases. Patients were enrolled beginning in November 2009 (18). Epidemiologic, demographic, and clinical data were collected by local physicians and anonymized. Independent ethics committee approval for enrolling patients was granted in accordance with local requirements. Written informed consent was obtained from patients (or from legal guardians in the case of patients who were minors) according to local ethics regulations. Two experts on MKD (AS and JF) checked the enrolled patient data for genetic, biochemical, and clinical characteristics. For this analysis, all cases enrolled until November 2014 were included. Patients harboring 2 *MVK* mutations or harboring 1 mutation in combination with an abnormal metabolic study result were considered to be true MKD patients. The metabolic criteria used were either increased urinary mevalonic acid or reduced mevalonate kinase enzyme activity in leukocytes or fibroblasts.

Response to different treatments (taken either intermittently based on current symptoms or on a regular basis) was classified as follows: complete response (complete control of the clinical manifestations and normalization of laboratory parameters), partial response (persistence of some clinical manifestations

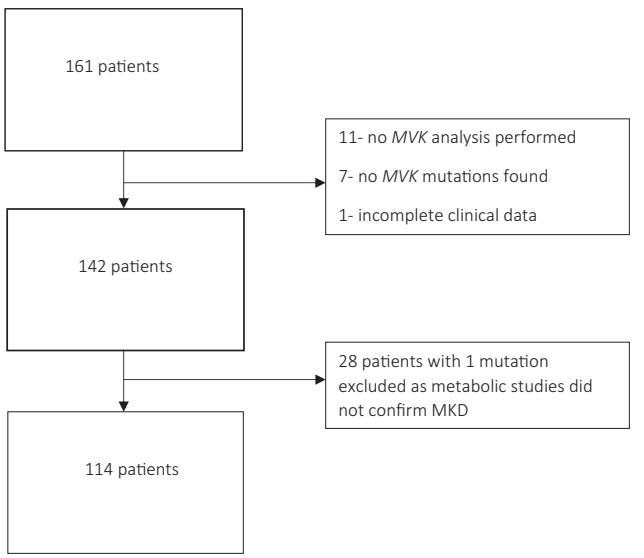

Figure 1. Flow chart of the inclusion of patients with mevalonate kinase deficiency (MKD) in the study.

and/or abnormal laboratory findings), or failure (absence of any substantial impact on disease activity or worsening).

Statistical analysis. All analyses were performed using SPSS 21. Categorical variables are presented as frequencies and percentages. Numeric variables are presented as the median and interquartile range (IQR). To determine a genotype–phenotype relationship, differences in clinical features between groups with specific genotypes were analyzed using Fisher's exact test. *P* values less than 0.05 were considered significant.

RESULTS

Demographic data. Up to November 2014, 161 patients had been enrolled by their local physicians in the Eurofever registry with a diagnosis of MKD. Nineteen of these patients were excluded because genetic testing had not been performed, no *MVK* mutations were found, or clinical data were incomplete. Another 28 patients with only 1 mutation were excluded since MKD could not be confirmed by demonstration of decreased mevalonate kinase activity or elevated urinary mevalonic acid excretion (Figure 1).

A total of 114 patients (53 male and 61 female) were enrolled from 31 centers in 12 countries. The majority of these patients were born in Italy (n = 31) and The Netherlands (n = 28) (Figure 2A). The median age at disease onset was 6 months (IQR 9 weeks to 19 months) (Figure 2B). The median age at diagnosis was 6.5 years (IQR 3.5–14.7 years). Thus, the median diagnostic delay was 6 years (IQR 1.9–14.2 years) (Figure 2C). The median follow-up period since age at onset was 11.5 years.

Genetic characteristics. Complete gene screening was performed in 47 (41%) of the patients, whereas in 46 (40%) of the patients only the most relevant exons

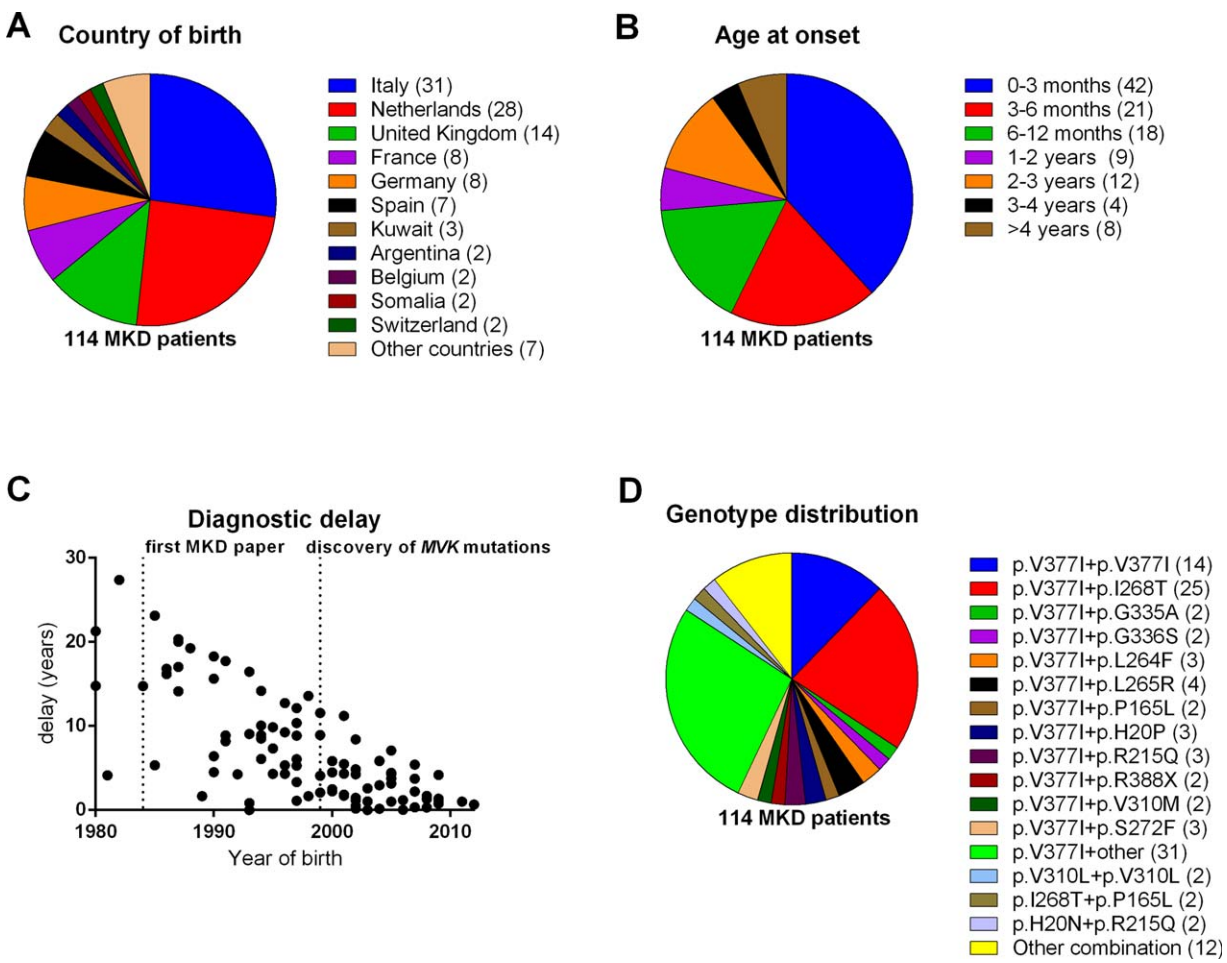

Figure 2. Characteristics of the 114 patients with mevalonate kinase deficiency (MKD). **A,** Country of birth of the MKD patients. Other countries included Albania, Australia, Cyprus, Czech Republic, Morocco, Russia, and Turkey. **B,** Age at onset of MKD. **C,** Diagnostic delay according to year of birth for patients born since 1980. **D,** Genotypes of all patients. In **A, B,** and **D,** the values in parentheses are the number of patients.

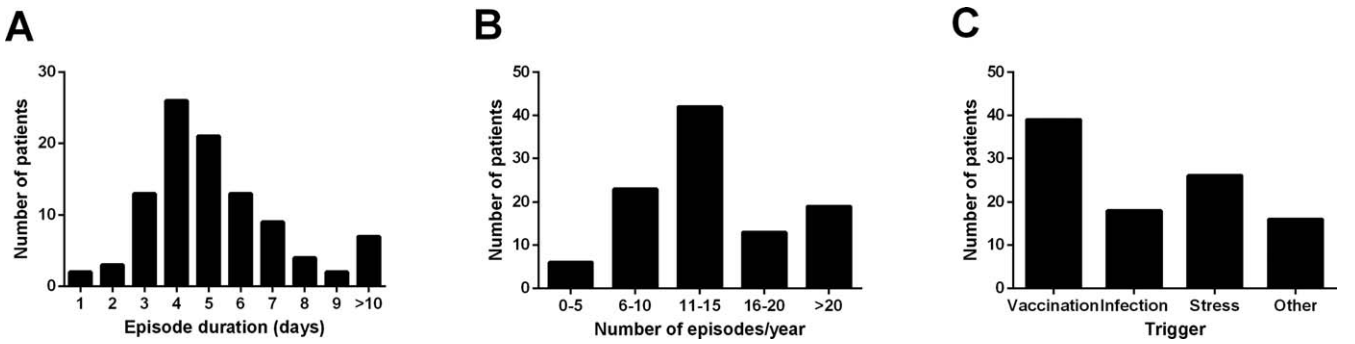

Figure 3. Features of inflammatory attacks in 108 patients with mevalonate kinase deficiency (MKD). **A,** Episode duration in days. **B,** Number of episodes per year. **C,** Episode triggers in 51 of the MKD patients. Other triggers included cold (n = 4), exercise (n = 5), trauma (n = 2), food (n = 1), menstruation (n = 4), fatigue (n = 6), and travel (n = 1).

Table 1. Clinical characteristics of the 114 patients with mevalonate kinase deficiency

	No. of patients/ no. assessed (%)	Patients with symptom present during every fever episode, %	Patients with symptom present during and between fever episodes, %
Disease pattern			
Recurrent	99/114 (87)	–	–
Continuous with exacerbations	9/114 (8)	–	–
Continuous	6/114 (5)	–	–
Constitutional symptoms*	79/111 (71)		
Malaise	70/108 (65)	53	23
Fatigue	69/109 (63)	52	35
Weight loss	16/102 (16)	–	–
Lymphoid organs	102/113 (90)		
Generalized enlargement	39/103 (38)	36	22
Cervical lymphadenopathy	96/113 (85)	64	15
Painful lymph nodes	59/99 (60)	42	12
Mucocutaneous involvement	99/113 (87)		
Aphthous stomatitis	67/111 (60)	37	15
Maculopapular rash	43/111 (39)	21	8
Urticarial rash	16/109 (15)	38	38
Exudative pharyngitis	31/109 (28)	16	10
Musculoskeletal involvement	89/113 (79)		
Arthralgia	80/113 (71)	34	15
Myalgia	64/112 (57)	34	18
Arthritis	31/109 (28)	24	9
Severe musculoskeletal involvement†	8/110 (7)		
Gastrointestinal symptoms	112/114 (98)		
Abdominal pain	98/111 (88)	44	16
Diarrhea	93/111 (84)	38	11
Vomiting	76/110 (69)	29	18
Severe gastrointestinal involvement‡	18/114 (16)		
Ocular involvement	17/113 (15)	–	–
Conjunctivitis	11/113 (10)	9	36
Uveitis	2/113 (2)	–	–
Impaired vision	2/113 (2)	–	–
Cataract	3/113 (3)	–	–
Neurologic involvement	46/114 (41)		
Headache	43/114 (38)	40	33
Mood disorders	23/95 (24)	43	25
Severe neurologic involvement§	6/114 (5)		

* Constitutional symptoms were defined as fever, malaise, fatigue, mood disorders, or weight loss.
† Severe musculoskeletal involvement was defined as flexion contractures, bone deformity, bone erosion, persistent arthritis, osteitis, or osteolytic lesion.
‡ Severe gastrointestinal involvement was defined as aseptic peritonitis, gastrointestinal bleeding, intestinal occlusion, gut perforation, abdominal adhesions, gastrointestinal ulcers, or perianal ulcers.
§ Severe neurologic involvement was defined as cerebellar syndrome, mental retardation, or aseptic meningitis.

were sequenced. In 4 (4%) of the patients only the most relevant point mutations were screened. Ninety-six (84%) of the patients harbored at least 1 p.V377I mutation, 14 (12%) of which were homozygous. The second most frequent mutation was p.I268T, occurring in 29 (25%) of the patients. None of them were p.I268T homozygous (Figure 2D).

Two mutations were not present in the Infevers database (19). A p.C152Y mutation was found in 1 patient. This patient also had a p.V377I mutation and had a mild clinical pattern, with no reported musculoskeletal or neurologic manifestations. Since this mutation was not known to be pathogenic, enzyme activity in both fibroblasts and leukocytes was assessed, and both assays showed decreased activity. Further, a 447_448insGCCTAC mutation, which is not known to be pathogenic, was found in 1 patient who also had a p.V377I mutation. This patient was not severely affected, and had mostly GI symptoms, myalgia, and lymphadenopathy. Metabolic studies were not performed.

Clinical characteristics. Ninety-nine of the 114 patients had recurrent disease episodes, i.e., they recovered completely between attacks. Six patients had continuous disease without clearcut exacerbations, whereas 9 patients had a continuous course with exacerbations. In these patients the intervals between attacks were characterized by some measure of ongoing inflammation. The median flare duration was 4 days, and the median flare frequency was 12 episodes per year (Figures 3A and B). Fever episodes were provoked by specific triggers in 51 patients, mainly by vaccination (n = 38), stress (n = 26), and infection (n = 18) (Figure 3C).

MKD symptoms and sequelae. *General features.* All clinical features are summarized in Table 1. Detailed descriptions of patients with severe manifestations can be found in Table 2. Seventy-nine patients had constitutional symptoms, such as malaise (n = 70), fatigue (n = 69), and weight loss (n = 16). In 23% of these patients, malaise was reported independent of fever, while fatigue occurred independent of fever in 35% of them. Constitutional symptoms independent of fever were not predictors of a more severe course such as amyloidosis. Most patients (n = 102) had lymphadenopathy, which was usually, but not exclusively, cervical (n = 96) and tender (n = 59). Generalized lymphadenopathy occurred in a sizeable minority (n = 39).

Mucocutaneous involvement. Ninety-nine patients had mucocutaneous symptoms, such as aphthous stomatitis (n = 67) and pharyngitis (n = 31). Fifteen percent of the patients had aphthous stomatitis independent of fever. Maculopapular rash (n = 43) and urticarial-like rash (n = 16) were seen between fever episodes in 8% and 38% of the patients, respectively.

Musculoskeletal involvement. Musculoskeletal symptoms were noted in 89 patients. Most had arthralgia (n = 80) or myalgia (n = 64), specifically during fever episodes (in 85% and 82% of the patients, respectively). Arthritis was less common (n = 31) and resolved when the fever episode subsided in 91%. In total, 8 patients had severe musculoskeletal involvement: flexion contractures (n = 5), persistent arthritis (n = 2), bone erosion (n = 2), osteolytic lesions (n = 2), osteitis (n = 2), and bone deformity (n = 1). These patients are described in more detail below and in Table 2.

One patient (patient 1) with persistent polyarthritis developed contractures and bone deformity. This patient also had severe GI symptoms, such as GI bleeding and GI and perianal ulcers. The other patient with persistent arthritis did not have other severe manifestations.

Two brothers, who had a compound heterozygous p.H20N and p.R215Q mutation, had flexion contractures, bone erosion, and osteolytic lesions. The older brother (patient 2) had involvement of 2 joints and also had severe GI involvement, including aseptic peritonitis, gut perforation, intestinal occlusion, and abdominal adhesions. In addition, he had scleritis. The younger brother (patient 3), who had continuous disease based on clinical features and chronic elevation of parameters of inflammation, had involvement of 13 joints. Joint contractures appeared at the age of 2 years.

Two patients had osteitis. One of them (patient 4) had a continuous disease pattern and had bacterial osteomyelitis. This patient also experienced aseptic peritonitis, intestinal occlusion, and abdominal adhesions. The other patient (patient 5) had osteitis without other severe manifestations. The osteitis was located in the right calcaneus. No bacterial growth was observed during blood culture. One patient had flexion contractures only.

GI involvement. GI symptoms were seen in 112 of the patients. Most of them experienced abdominal pain (n = 98), diarrhea (n = 93), and vomiting (n = 76). In >80% of these patients, these symptoms were only seen during fever episodes. Eighteen patients had severe GI symptoms: aseptic peritonitis (n = 7), GI bleeding (n = 7), perianal ulcers (n = 5), intestinal occlusion (n = 3), gut perforation (n = 2), and GI ulcers (n = 2).

Abdominal adhesions were reported in 4 patients, although the modality of identification of this complication (imaging or after surgery) was not specified. Two sisters (patients 6 and 7) both had GI bleeding. The older sister also had uveitis and scleritis, while the younger sister had flexion contractures.

Table 2. Severely affected patients with MKD*

Patient	Severe manifestations	Mutation 1	Mutation 2	Age at onset, years	Diagnostic delay, years	Disease course	Episode duration, days	Biologic agents received (treatment response)
1	Musculoskeletal, gastrointestinal	p.H20Q	p.H20Q	0.2	0.2	Recurrent	4	Etanercept (partial response)
2	Musculoskeletal, gastrointestinal, ocular	p.H20N	p.R215Q	0.1	14.8	Recurrent	5	Anakinra maintenance (complete response), etanercept (partial response)
3	Musculoskeletal	p.H20N	p.R215Q	0	4.5	Continuous	NA	Anakinra (partial response), etanercept (treatment failure)
4	Musculoskeletal, gastrointestinal	p.P165L	p.I268T	0	1.5	Continuous	NA	Anakinra maintenance (partial response), etanercept (treatment failure)
5	Musculoskeletal	p.V377I	p.S329R	7.8	0	Recurrent	4	Canakinumab (complete response), etanercept (partial response)
6	Gastrointestinal, ocular	p.V310L	p.V310L	3.3	23.1	Continuous	NA	None
7	Musculoskeletal, gastrointestinal	p.V310L	p.V310L	3	14.2	Continuous	NA	Anakinra maintenance (partial response)
8	Gastrointestinal	p.G336S	p.N166I	4.9	36.1	Recurrent	7	None
9	Gastrointestinal	p.V377I	p.I268T	0.1	26.9	Recurrent	4	Anakinra during attacks (partial response), etanercept (partial response)
10	Gastrointestinal, neurologic	p.T237S	p.I268T	0.01	0.7	Continuous	NA	None
11	Neurologic, ocular	p.A334T	p.A141fs	0.01	2.1	Recurrent	4	Anakinra maintenance (treatment failure)
12	Neurologic	p.V377I	p.V377I	0.5	5.5	Recurrent	4	None
13	Neurologic	p.P165L	p.I268T	0.3	5.4	Recurrent	No specific pattern	Anakinra during attacks (partial response)
14	Neurologic	p.V377I	c.606insG	0.3	1.2	Recurrent	3	None
15	Neurologic	p.V377I	p.I268T	0.6	1.1	Recurrent	5	None
16	MAS, ocular	p.V377I	del exon 8	2	4.3	Recurrent	5	Anakinra (partial response), canakinumab (complete response)
17	Amyloidosis	p.V377I	p.L234P	2.1	41.1	Recurrent	6	Anakinra during attacks (partial response), etanercept (partial response), tocilizumab (partial response)
18	Amyloidosis	p.V377I	p.I268T	4	23.7	Recurrent	Not known	None
19	Amyloidosis	p.V377I	p.I268T	4	14.8	Recurrent	10	Anakinra maintenance (partial response), etanercept (treatment failure), tocilizumab (complete response)
20	Amyloidosis	p.V377I	p.I268T	3	24.5	Recurrent	13	Anakinra maintenance (partial response)
21	Amyloidosis	p.V377I	p.I268T	0.1	17.7	Continuous	NA	None

* MKD = mevalonate kinase deficiency; NA = not applicable; MAS = macrophage activation syndrome.

Patient 8 had aseptic peritonitis and perianal ulcers. Another patient (patient 9) had aseptic peritonitis and abdominal adhesions. One patient (patient 10), who had a continuous disease course, had aseptic peritonitis, GI bleeding, gut perforations, and abdominal adhesions. This patient also experienced aseptic meningitis. She died due to acute respiratory distress syndrome before the age of 1 year. Ten additional patients had 1 severe GI manifestation, namely, GI bleeding (n = 3), perianal ulcers (n = 3), aseptic peritonitis (n = 2), intestinal occlusion (n = 1), or GI ulcers (n = 1), without other severe organ involvement.

Neurologic involvement. Headache was the most common neurologic symptom (n = 43) and was reported independent of fever in 33% of the patients. Mood disorders were reported in 23 patients. Moreover, 25% of these patients had mood disorders between fever episodes, thus reflecting the psychological impact of the disease, irrespective of its recurrent or continuous course. Six patients had severe neurologic manifestations, namely, mental retardation (n = 4), cerebellar syndrome (n = 2), and aseptic meningitis (n = 1). One patient (patient 11), who had a recurrent disease course, experienced both a cerebellar syndrome and mild mental retardation. This patient also had retinitis pigmentosa and has been described before in a case report (20). Another patient (patient 12) who had cerebellar disease also had a recurrent disease course. He was diagnosed as having type 1 Arnold-Chiari cerebellar syndrome as an incidental finding upon magnetic resonance imaging of the brain performed at the age of 2 years. Despite this malformation, he showed normal psychomotor development. He had a twin who died in utero. One patient (patient 13) with mental retardation was heterozygous for p.I268T and p.P165L and had colitis as part of the MKD. The 2 other patients with mental retardation (patients 14 and 15) had no other severe manifestations.

Macrophage activation syndrome (MAS). MAS occurred in 1 patient (patient 16) who had a heterozygous p.V377I and deletion in exon 8 mutation (p.Arg226fs). This patient has been described previously (21). At that time, the patient was receiving only flurbiprofen at full dosage, and the disease was apparently well controlled. The MAS presented initially as a typical MKD episode with high fever, arthralgia, myalgia, and oral aphthae, which led to hospitalization. Two days after hospitalization, the patient was treated with several antibiotics due to presumed sepsis. The clinical picture worsened, with initial heart failure and lethargy. Intensive care support with continuous ventilation was required. Bone marrow aspiration revealed activated macrophages and numerous hemophagocytic cells. The patient was treated with high-dose methylprednisolone (30 mg/kg/day) for 4 days. Thereafter, maintenance steroid therapy (1 mg/kg/day) and cyclosporine (4 mg/kg/day) were given.

AA amyloidosis. AA amyloidosis was diagnosed in 5 patients. The median delay to the diagnosis of MKD in these 5 patients was 23 years (range 15–41 years). The median disease duration before the diagnosis of amyloidosis was 23 years (range 8–37 years).

One of these 5 patients (patient 17) had a p.V377I mutation in combination with a p.L234P mutation. He presented with end-stage renal failure at the age of 39 years and also had involvement of the liver and spleen. A renal transplantation was performed 2 years after the diagnosis of amyloidosis, with good graft function.

The other 4 patients (patients 18–21) were compound heterozygous for the p.V377I mutation and the p.I268T mutation. In 1 of these 4 patients (patient 18), AA amyloidosis presented with end-stage renal failure at the age of 27 years and was diagnosed by biopsy, showing involvement of the kidneys and spleen. She had persistent inflammation with continuously elevated parameters of inflammation. She died at the age of 45 years due to complications after 18 years of dialysis.

Patient 19 presented with end-stage renal failure at the age of 19 years. Serum amyloid P (SAP) component scintigraphy showed involvement of the kidneys, spleen, and liver. He received renal transplants from living related donors twice. The first kidney was lost due to recurrent amyloid deposition. The second transplantation led to good graft function. After the first renal transplantation, the disease was not well controlled with anakinra and subsequently etanercept. During a period of 5 years, the patient did not receive any biologic agent. Four months before the second transplantation, treatment with tocilizumab was started, with complete response. In his brother (patient 20), amyloidosis was diagnosed at the age of 37 years, after presentation with end-stage renal failure. SAP scintigraphy showed involvement of the kidneys, spleen, and liver. He received a renal transplant from a living related donor a year after diagnosis, with good results.

The last patient (patient 21) was diagnosed as having amyloidosis at the age of 8 years. Treatment with colchicine was started due to suspected familial Mediterranean fever. At the age of 12 years she underwent kidney transplantation. When she was 18 years old, she was diagnosed as having MKD. She died at the age of 19 years.

Table 3. Associations between genotype and clinical characteristics of the patients with MKD*

Phenotype	Patients with p.V377I and p.V377I (n = 14)	Patients with p.V377I and p.I268T (n = 25)	Patients with p.V377I and other mutation (n = 57)	Patients without p.V377I (n = 18)	*P*
Continuous course	0	4	0	28	0.000†
Family history	45	38	29	53	NS
Constitutional symptoms	85	68	85	89	NS
Mucocutaneous involvement	100	76	91	78	NS
Gastrointestinal involvement	100	96	100	94	NS
Severe gastrointestinal involvement	0	16	12	39	0.02†
Lymphoid involvement	93	92	89	89	NS
Ocular involvement	21	8	11	35	NS
Neurologic involvement	64	48	30	47	NS
Severe neurologic involvement	14	4	2	20	NS
Musculoskeletal involvement	86	64	77	100	0.025†
Severe musculoskeletal involvement	0	0	4	33	0.001†
Amyloidosis	0	16	2	0	0.049‡

* Values are the percent of patients. MKD = mevalonate kinase deficiency; NS = not significant.
† Patients without p.V377I versus all other groups, by Fisher's exact test.
‡ Patients with p.V377I and p.I268T versus all other groups, by Fisher's exact test.

Laboratory findings. Abnormal IgD levels were found in 55 of 76 patients assessed. Other Ig levels were also measured. IgA levels were elevated in 48 of 90 patients, while IgG levels were elevated in 14 of 91 patients. IgM levels were within the normal range in 81 of the 91 patients tested.

Measurement of urinary mevalonic acid was performed in 40 patients; 37 of them showed elevated excretion. Thus, 3 patients excreted normal amounts of mevalonic acid. All 3 of these patients had typical MKD symptoms. The first patient was homozygous for p.V377I and had confirmed impairment of mevalonate kinase enzyme activity. Urine was collected during a fever episode. This patient has been described before in a diagnostic study (22). The second patient was compound heterozygous for p.R388X and stop397R. In this patient mevalonic acid was measured as part of whole organic acid screening. It is unknown whether the patient was well or febrile during urine sampling. The last patient was compound heterozygous for p.V377I and p.V310M and had a mild clinical pattern. In this patient urine was not collected during a fever episode.

Enzymatic studies in both leukocytes and fibroblasts were performed in 19 patients. Reduced mevalonate kinase enzyme activity in fibroblasts was found in 7 of 8 patients tested, while 15 of 16 patients tested showed reduced enzyme activity in leukocytes. Unexpectedly, 1 patient with a homozygous p.V377I mutation, typical MKD symptoms, and elevated urinary mevalonic acid excretion exhibited normal enzyme activity in both fibroblasts and leukocytes.

Associations between genotype and phenotype. To analyze genotype–phenotype associations, we divided all patients into 4 groups: patients who were homozygous for p.V377I; patients who were compound heterozygous for p.V377I and p.I268T; patients with 1 p.V377I mutation and a second mutation other than p.V377I or p.I268T; and patients without a p.V377I mutation. The frequency of MKD features was compared between the groups. Four of the 25 patients with p.V377I/p.I268T combined heterozygosity experienced amyloidosis, as compared to 1 of 89 patients with other genotypes ($P = 0.049$). Further, patients with mutations other than a p.V377I mutation more often had a continuous disease course, musculoskeletal involvement, severe musculoskeletal involvement, and severe GI involvement (Table 3).

Treatment. *Nonsteroidal antiinflammatory drugs (NSAIDs).* NSAIDs were administered to 66 patients, usually to treat the symptoms of attacks, and were beneficial in 48 of them. Seven of these patients exhibited a complete response to NSAIDs. Five of them took NSAIDs during attacks only and not as maintenance therapy. Two of them received NSAIDs as monotherapy, and the other 5 received NSAIDs in combination with corticosteroids. The response to steroids was reported as complete in 4 of the patients and as partial in 1 patient.

Corticosteroids. Corticosteroids were given to 49 patients to treat fever attacks. Complete suppression of inflammatory episodes was reported for 19 of them (16

of the 19 had not received biologic agents), and some improvement was reported for 21 patients. Five of 7 patients who received maintenance corticosteroids experienced some benefit; failure to respond was noted in the other 2.

Colchicine and statins. Colchicine was received by 21 patients; 13 of them did not respond to this treatment, and only 1 patient, who was heterozygous for p.V377I and p.S135L, had a complete response. Familial Mediterranean fever (*MEFV*) screening had not been performed in this Caucasian patient from Italy. The patient did not receive NSAIDs, steroids, or biologic agents. Statins were used to treat 15 patients; in 11 patients this treatment failed. Moreover, 3 of them experienced worsening of their disease. Four patients noted some improvement of symptoms.

Biologic agents. Eight patients received anakinra only during attacks, with 3 of them having a complete response and the other 5 a partial response. Nineteen patients received anakinra as maintenance therapy, which led to complete remission in 3 of them and a partial response in 13. In 3 patients anakinra was not effective. All 3 had a recurrent disease pattern. One of them was severely affected and had cerebellar syndrome, mental retardation, and retinitis pigmentosa. The 2 other patients were mildly affected and did not have severe manifestations. In at least 7 patients with an initial failure to respond or partial response to anakinra, the dose of anakinra was increased. This increase in dose did not lead to complete remission. Four of these 7 patients have switched to another therapy, and 3 of them are still receiving anakinra. In another 6 patients with an initial partial response to anakinra, the dose was not increased. Three of them are still receiving anakinra.

Five patients were treated with canakinumab; complete remission was achieved in 4 of them, and 1 had a partial response. The patient with a partial response was p.V377I/p.G338D compound heterozygous with disease that had failed to respond to NSAIDs, steroids, anakinra, etanercept, and adalimumab before the initiation of canakinumab. Two patients with a complete response had had a partial response to anakinra before treatment with canakinumab.

Etanercept was prescribed to 27 patients. It had a beneficial effect in 16 patients, of whom 2 had a complete response. Disease failed to respond to etanercept in 11 patients.

DISCUSSION

This report presents the phenotypic and genotypic characteristics and the response to treatment in the largest cohort of MKD patients described so far. Moreover, the vast majority (87 of these patients) have not been described in previous cohorts (10,23). This large cohort enables us to provide a broad description of the clinical features and treatment of this rare disease.

In many respects, our study confirms the clinical characteristics described in previous reports. Typically, the disease starts within the first year of life. Onset after the age of 4 years makes the diagnosis extremely unlikely. The most common symptoms were fever, abdominal pain, diarrhea, vomiting, lymphadenopathy, arthralgia, myalgia, and aphthous stomatitis. Five patients had AA amyloidosis, a frequency almost twice that reported in previous cohorts (23). This might be due to reporting bias, since these patients are more likely to be enrolled in the registry. Still, this number might be an underrepresentation due to the limited follow-up period. The median age of enrolled patients was only 12 years, while amyloidosis occurred after 18 years in 4 of the 5 patients. Only 1 patient in our cohort experienced MAS, which is fewer than in the study by Bader-Meunier et al (10).

Many patients had symptoms between attacks. These included mainly constitutional symptoms, such as fatigue, malaise, and headache, but also oral aphthous ulcers. It has to be noted that these symptoms are also very common in the general population and have been seen at increased frequencies in patients with rheumatic diseases (24,25). In our cohort, patients with constitutional symptoms between attacks did not have a more severe course such as amyloidosis.

According to the enrolling centers, up to 25% of the patients displayed some mood disorders. In the original survey, the definition of mood disorders was left to the discretion of the enrolling physicians. However, this relatively high frequency possibly reflects the psychological impact of the disease, as previously reported by van der Hilst et al (23).

Although uncommon, some patients in our series did have severe musculoskeletal manifestations, such as persistent arthritis. In these severe cases, the differentiation between MKD and other pediatric rheumatic diseases such as systemic juvenile idiopathic arthritis (JIA) can be difficult. However, the disease course with frequent, short attacks of fever alternating with prolonged episodes of spontaneous remission renders diagnoses like systemic JIA highly unlikely.

This study confirms previous findings that measurement of IgD is not a reliable method to diagnose MKD (15), since 28% of the patients tested in this cohort did not have elevated IgD levels. Further, measurement of urinary mevalonic acid is a sensitive method

of MKD screening, as 93% of the patients tested excreted elevated amounts of mevalonic acid (10,22). The failure to detect mevalonic acid in some patient samples may be due to methodologic limitations, since isotope dilution was not used in all of these patient samples. Unexpectedly, in 1 patient, mevalonate kinase enzyme activity was reportedly entirely normal in the presence of known pathogenic mutations and elevated urinary excretion of mevalonic acid. Enzymatic studies have been regarded as the diagnostic gold standard for MKD (8). However, apparently even enzyme activity assays may yield false-negative results.

The most frequent combination of mutations was p.V377I/I268T heterozygosity, occurring in 22% of the patients, followed by p.V377I homozygosity in 12%. Patients with a combined heterozygosity for p.V377I/p.I268T had AA amyloidosis significantly more often.

As reported previously (23,26), treatment with statins and colchicine was not effective in most patients. Seventy-five percent of the patients experienced at least some benefit when using NSAIDs, but efficacy was rarely complete. Corticosteroids are more effective for terminating inflammatory attacks, but long-term side effects are a major drawback. Interleukin-1 (IL-1) blockade is beneficial in many MKD patients, but apparently not as effective as observed in the IL-1–driven cryopyrin-associated periodic syndromes (26). Although the number of MKD patients in the present study is substantially higher than that in a previous study on therapy in the Eurofever cohort (26), the findings regarding therapy remain essentially unchanged. Some patients did not benefit from the use of biologic agents. From the available data, the possibility that these patients received an insufficient dose cannot be excluded. However, in 7 patients, an increase in the anakinra dose did not result in the complete control of symptoms.

The retrospective design of the Eurofever registry comes with a number of limitations. Due to this design, there were a number of variables reported as "not known" by the centers. This was mainly due to the fact that some variables requested by the Eurofever registry could not be retrieved from the clinical chart, because they were not investigated at the time of the patients' evaluation. This issue might have introduced a bias, with a possible underrepresentation of some symptoms. For that reason, we have chosen to use the number of known values as the denominator in the tables.

Further, the Eurofever Registry collects data on patients with periodic fever. The participating physicians are pediatric immunologists and pediatric rheumatologists. Since patients with mevalonic aciduria experience predominantly neurologic symptoms, these patients are more likely to be seen by a pediatric neurologist or a specialist in metabolic diseases. Therefore, some of the more severely affected MKD patients may not have been enrolled. In addition, patients with mevalonic aciduria may be underrepresented since they are more likely to die at a young age (12). Still, our cohort included some patients who could be classified as having mevalonic aciduria. Also, many patients were enrolled by European centers since the Eurofever registry is predominantly known in Europe.

Finally, the involvement of more pediatric than adult specialists may have introduced an age bias. MKD does not seem to carry a high mortality rate, yet the median age of enrollment in our cohort was 12 years. A long follow-up period is needed to acquire information about long-term complications. A limitation to the interpretation of therapeutic interventions is the absence of clear criteria for complete and partial response. The response was left to the interpretation of the physician. Bias is inevitable due to the lack of control groups and randomization. Furthermore, since it is unknown whether drugs were used simultaneously or sequentially, it is even more difficult to draw solid conclusions about the efficacy of treatments. However, the Eurofever registry does provide information on current practice.

In conclusion, we have described the clinical and genetic features in the largest international cohort of MKD patients to date. Most MKD patients experienced fever, accompanied by GI symptoms, lymphadenopathy, arthralgia, and aphthous stomatitis. AA amyloidosis (occurring in 4% of the patients) and MAS (occurring in 0.9% of the patients) were rare, but severe, complications of MKD. Some patients benefited from treatment with NSAIDs, steroids, or biologic agents, mainly IL-1 blockers and etanercept. Statins and colchicine were usually not effective in treating MKD.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Frenkel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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